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Bolus Intravenous Nitroglycerin Predominantly Reduces Afterload in Patients With Excessive Arterial Elastance

HOWARD L. HABER, MD, CHRISTOPHER L. SIMEK, MD, JAMES D. BERGIN, MD, FACC, ALBERTO SADUN, PHD, LAWRENCE W. GIMPLE, MD, FACC, ERIC R. POWERS, MD, FACC, MARC D. FELDMAN, MD, FACC

Charlottesville, Virginia

Objectives. **We hypothesized that bolus intravenous nitroglycerin would be an afterload-reducing agent in patients with excessive initial afterload for their level of left ventricular systolic function. Conversely, bolus intravenous nitroglycerin should be a preload-reducing agent in patients without excessive initial afterload.**

Background. **Although nitroglycerin has both preload- and afterload-reducing actions, methods to predict its predominant site of action in an individual patient have not been previously described.**

Methods. **Left ventricular pressure-volume relation were recorded with micromanometer and conductance catheters during bolus injection of intravenous nitroglycerin in 27 patients with both normal left ventricular systolic function and varying degrees of congestive heart failure. Preload was determined by end-diastolic volume, afterload by effective arterial elastance, left ventricular systolic function by end-systolic elastance and coupling of afterload and ventricular function by the ratio of effective arterial elastance to end-systolic elastance (E_a/E_{es} ratio). An E_a/E_{es} ratio >1 was defined as excessive afterload for the level of ventricular function.**

Results. **Patients with an initial E_a/E_{es} ratio <1 (Group 1) constituted a group of normotensive patients with intact ventricular function who exhibited a predominant reduction in preload in response to intravenous nitroglycerin. Those with an initial E_a/E_{es} ratio >1 and normal or mildly depressed ventricular function (Group 2a) constituted a group of patients, most of whom were hypertensive, who exhibited a predominant afterload reduction. Finally, those with an initial E_a/E_{es} ratio >1 and abnormal ventricular function (Group 2b) constituted a group of patients with clinical congestive heart failure who exhibited both preload and afterload reduction but a predominant afterload reduction because stroke volume increased.**

Conclusions. **Patients with normal arterial elastance and ventricular function respond to nitroglycerin with a predominant preload reduction, whereas patients with either excessive arterial elastance or abnormal ventricular function respond with a predominant afterload reduction.**

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Despite the clinical application of nitroglycerin since the 19th century, its predominant site of action on the peripheral circulation is still controversial. The benefit of nitroglycerin therapy has historically been believed to be mediated through venodilation, with subsequent preload reduction. More recently, the arteriolar dilating actions of nitroglycerin have been recognized (1–11).

Although nitroglycerin has both preload-reducing and afterload-reducing actions, methods to predict its predominant site of action in a given patient using left ventricular pressure-volume relations have not been previously described. Left ventricular pressure-volume relations allow the relations among preload (end-diastolic volume), afterload (effective arterial elastance [E_a]) and left ventricular systolic function (end-systolic elastance [E_{es}]) to be quantitated. Furthermore, Sunagawa et al. (12,13) have demonstrated that maximal mechanical energy is transferred from the ventricular to the arterial system when effective arterial elastance and end-systolic elastance are equal, allowing coupling of the ventricular and arterial systems. We hypothesized that bolus intravenous nitroglycerin would be primarily an afterload-reducing agent in patients with excessive initial afterload (E_a) for their level of left ventricular systolic function (E_{es}). Conversely, nitroglycerin should primarily be a preload-reducing agent in patients without excessive initial afterload (E_a) for their level of left ventricular systolic function (E_{es}). To test this hypothesis, left ventricular pressure-volume relations were recorded during bolus intravenous nitroglycerin administration in patients with normal left ventricular systolic function who had varying degrees of congestive heart failure. We then determined end-diastolic volume, effective arterial elastance, end-systolic elastance

From the Division of Cardiology, Department of Internal Medicine, University of Virginia Health Sciences Center, Charlottesville, Virginia. This study was supported by a fellowship to Dr. Haber from the American Heart Association, Virginia Affiliate, Inc. (VA-91-F-61) and a FIRST Award (R29HL47046-01) to Dr. Feldman from the National Heart, Lung, and Blood Institute of the National Institutes of Health, Bethesda, Maryland.

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Address for correspondence: Marc D. Feldman, MD, Box 158, Division of Cardiology, University of Virginia Health Sciences Center, Charlottesville, Virginia 22908.

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and the relation of effective arterial elastance to end-systolic elastance (E_a/E_{es} ratio) before and after bolus intravenous nitroglycerin.

Methods

Study patients. Twenty-seven patients were enrolled in this study, 24 men and 3 women with a mean age ± SEM of 57 ± 4 years. Eighteen did not have a history of congestive heart failure (left ventricular ejection fraction 66 ± 4%, range 41% to 93%), and an additional nine patients had clinical congestive heart failure (New York Heart Association functional classes II to IV, left ventricular ejection fraction 24 ± 4%, range 11% to 39%). Patients without a clinical history of congestive heart failure were referred for cardiac catheterization for a chest pain syndrome and had no history of congestive symptoms. Of these patients, eight had epicardial coronary artery disease and nine had a history of hypertension. Of the patients with congestive heart failure, the cause was idiopathic dilated cardiomyopathy in four patients and ischemic cardiomyopathy in five. Three patients with and nine patients without congestive heart failure had a history of hypertension. All medications were withheld 18 h before cardiac catheterization, with the exception of diuretic agents in patients with congestive heart failure. Written informed consent was obtained from each patient, and the protocol was approved by the Human Investigation Committee at the University of Virginia.

Data acquisition. *Conductance catheter technique.* A full description of the conductance catheter has been published elsewhere (14–16). The present study was performed with an 8F conductance catheter (Webster Labs) and, fully extended within its lumen, a 2F micromanometer catheter (Millar Instruments). The catheter is positioned under fluoroscopic guidance along the long axis of the left ventricle and connected to a digital stimulator microprocessor (Sigma V, Leycom). The system uses a dual excitation algorithm and two pairs of stimulating electrodes (single field). Resistance differences between intervening electrode pairs are inversely related to segmental volumes, and individual segment volumes are summed to yield total chamber volume. Real-time pressure-volume loop display and two-channel analog/digital conversion (at 200 Hz) were performed using a 16-bit microcomputer system (Halcom, Inc).

Protocol. Routine right and left heart catheterization was performed with the Judkins technique. Nonionic contrast medium was used (Isovue, Squibb Diagnostics) to minimize negative inotropic effects. Fifteen minutes was allowed to elapse between coronary angiography and left ventriculography and initiation of the research protocol. Baseline hemodynamic determinations, including heart rate, pulmonary capillary wedge and left ventricular pressures, were recorded. Five determinations of thermodilution cardiac output were made for later gain adjustments of conductance stroke volume. A 5-ml sample of venous blood was taken for baseline determination of blood resistivity (ρ). After placement of the 8F conductance and 2F Millar catheters, as outlined earlier, an intravenous bolus of nitroglycerin was administered by way of the femoral vein, and left ventricular volume and pressure were recorded for 40 s on a beat by beat basis.

Nitroglycerin dose. The dose of nitroglycerin was chosen so that drug administration resulted in at least a 15-mm Hg decrease in systolic arterial pressure. This dose of bolus intravenous nitroglycerin was determined in previous pilot studies to be 200 μg in patients with no congestive heart failure (Groups 1 and 2a) and 400 μg in patients with a clinical history of congestive heart failure and a reduced ejection fraction at the time of catheterization (Group 2b). In these pilot studies, a dose <400 μg did not produce a reliable decrease in systolic arterial pressure in all patients with congestive heart failure, and end-systolic elastance could not be calculated accurately using a lower dose. Peripheral resistance decreases due to the immediate effects of nitroglycerin administration in patients with congestive heart failure have been previously described (17,18).

Data analysis. Data obtained from the conductance and micromanometer catheters were analyzed off-line by computer (Halcom, Inc.). Pressure and volume recordings were smoothed with a three-point, nonweighted moving average before hemodynamic variables were determined. Raw volume measurements from the conductance catheter were calibrated with a correction for offset and gain. For offset correction, the end-diastolic volume of the baseline conductance volume signal was set equal to the right anterior oblique left ventriculogram end-diastolic volume (19). For gain calibration, the conductance volume signal was multiplied by the ratio of themodilution stroke volume and conductance stroke volume.

The pressure-volume ramp used to generate end-systolic elastance began 1 beat preceding a visual decrease in pressure or volume and ended with the first beat of the nadir pressure or volume or baroreflex activation (defined as a 5% increase in heart rate on 3 consecutive beats). All premature and postpremature beats were excluded from the analysis. Baseline end-diastolic volume, effective arterial elastance and stroke volume were determined from the mean of 3 consecutive beats immediately preceding this pressure-volume ramp. The effect of bolus nitroglycerin on end-diastolic volume, effective arterial elastance and stroke volume was determined at the nadir pressure or volume. If a reflex increase in heart rate occurred before nadir pressure or volume, then end-diastolic volume, effective arterial elastance and stroke volume were determined from the beat immediately before reflex activation.

End-systolic elastance. The end-systolic pressure (P)-volume (V) point of each loop was selected as the data point with the maximal pressure-volume ratio. A least-squares linear regression of these points was applied, generating slope (E_{es}) and intercept (V_0) estimate. With this estimate of intercept, points of maximal $P/V - V_0$ for each cycle were

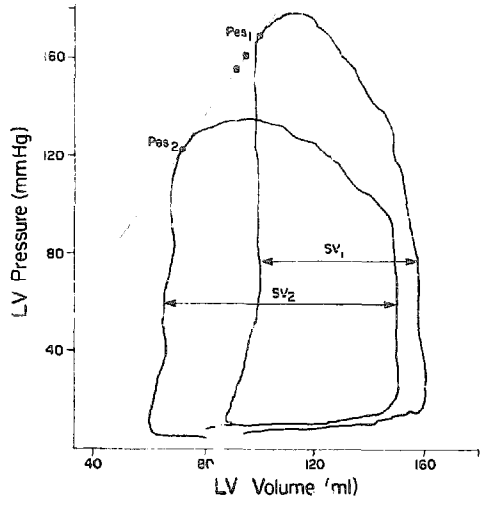


Figure 1. Calculation of effective arterial elastance (E_a) on a beat by beat basis. Effective arterial elastance is calculated from the ratio of left ventricular (LV) end-systolic pressure (Pes) to stroke volume (SV) for each pressure-volume relation. In this example, $E_{a1} > E_{a2}$ because $P_{es1} > P_{es2}$, and $SV_1 < SV_2$.

obtained, and an iterative regression analysis was performed until both slope and intercept remained constant.

Effective arterial elastance (Fig. 1). Arterial elastance is a lumped variable combining compliance, characteristic impedance and resistive properties of the vasculature. Because resistive properties predominate, it is approximately equal to the product of systemic vascular resistance and heart rate. Because heart rate remains constant for all pressure-volume relations analyzed for each patient, effective arterial elastance approximated systemic vascular resistance. Effective arterial elastance was calculated from the ratio of end-systolic pressure (P_{es}) and stroke volume (SV), or $E_a = P_{es}/SV$, as previously defined (12,13,20).

By representing arterial load as an effective elastic chamber, effective arterial elastance allows arterial and ventricular properties to be coupled. Optimal effective arterial elastance to end-systolic elastance has been previously defined as a ratio near unity (13). For the current study, patients were classified into groups according to their baseline E_a/E_{es} ratio. An E_a/E_{es} ratio >1.0 was defined as excessive afterload for the level of ventricular function.

Definition of predominant preload or afterload effect. To characterize the hemodynamic effects of bolus intravenous nitroglycerin, measurements of preload, afterload and stroke volume were made before and after nitroglycerin administration. Left ventricular preload was measured by left ventricular conductance end-diastolic volume, whereas left ventricular afterload was measured by effective arterial elastance. In some patients, both preload and afterload were reduced after bolus intravenous nitroglycerin administration. To determine which reduction predominated, calibrated conductance stroke volume was utilized. A decrease in preload was considered predominant if stroke volume decreased and decrease in afterload was considered predominant if stroke volume increased.

Table 1. Classification of Study Groups

Study Group	E_a/E_{es} Ratio	EF
1	<1	*
2a	>1	>40%
2b	>1	<40%

*All patients with E_a/E_{es} ratio <1 had an ejection fraction ≥50%. E_a = effective arterial elastance; EF = ejection fraction; E_{es} = end-systolic elastance.

Statistical analysis. Data were compiled and analyzed on a minicomputer (VAX 8200, Digital Equipment Corp.) using RS/1 (Bolt, Beraneck and Newman). Continuous variables were expressed as mean value ± SEM, and differences between groups were estimated by means of either the *t* test with pooled variance with a Bonferroni correction for multiple comparisons or one-way analysis of variance (ANOVA). Categoric data were expressed as proportions, and differences between groups were estimated using the Fisher exact test. Differences between groups were considered significant at a p value < 0.016 (two-tailed).

Results

Patient subset stratification (Table 1). Patients were stratified into groups according to their initial E_a/E_{es} ratio. Group 1 (n = 9) those patients comprised with an E_a/E_{es} ratio <1, representing those whose baseline afterload was low for their level of ventricular function. Group 2 (n = 18) was defined as those patients with an E_a/E_{es} ratio >1, representing those with excessive afterload for their level of ventricular function. This group included some patients with normal or mildly depressed left ventricular ejection fraction (Group 2a, n = 9) and all patients with reduced ventricular function (congestive heart failure) (Group 2b, n = 9). Similar numbers of patients in all three groups were treated with calcium channel blocking agents, beta-adrenergic blocking agents and long-acting oral nitrates before the withdrawal of medications at least 18 h before study. However, more patients in Group 2b than in either Group 1 or 2a were treated with angiotensin-converting enzyme inhibitors (six vs. one and one, respectively, p = 0.02).

Baseline hemodynamic characteristics (Table 2). Left ventricular systolic function, as indicated by both left ventricular ejection fraction and end-systolic elastance, was greatest in patients in Group 1. Patients in Group 2a had higher effective values for arterial elastance than did patients in Group 1, consistent with their higher incidence of clinical hypertension (eight of nine, 89%), but they had lower end-systolic elastance values than those observed in patients in Group 1. Patients in Group 2b had higher values for rest heart rate and pulmonary wedge pressure, lower values for left ventricular ejection fractions and end-systolic elastance

Table 2. Baseline Hemodynamic and Clinical Characteristics of Patients in the Three Study Groups

Study Group	HR (beats/min)	PCW (mm Hg)	LVSP (mm Hg)	EF (%)	E_{es} (mm Hg/ml)	E_a (mm Hg/ml)	HTN	CHF
1 (E_a/E_{es} < 1) (n = 9)	68 ± 4	14 ± 2	142 ± 6	69 ± 4	2.25 ± 0.22	1.57 ± 0.15	2 (22)	0 (0)
2a (E_a/E_{es} > 1; EF > 40%) (n = 9)	74 ± 3	13 ± 1	159 ± 9	57 ± 3	1.49 ± 0.12*	2.75 ± 0.45*	8 (88)*	0 (0)
2b (E_a/E_{es} > 1; EF < 40%) (n = 9)	88 ± 3*	26 ± 4*	128 ± 7	24 ± 4*	0.77 ± 0.22*†	3.70 ± 0.36*	3 (33)	9 (100)*†

*p < 0.005 versus Group 1. †p < 0.016 versus Group 2a. Values are expressed as mean value ± SEM or number (%) of patients. CHF = congestive heart failure; HR = heart rate; HTN = hypertension; LVSP = left ventricular systolic pressure; PCW = pulmonary capillary wedge pressure; other abbreviations as in Table 1.

and higher values for effective arterial elastance than did patients in other groups.

Hemodynamic response to bolus nitroglycerin (Table 3, Fig. 2). Changes in left ventricular end-diastolic volume (preload) were different in all three groups (p = 0.04 by ANOVA). End-diastolic volume was reduced most in Group 1, least in Group 2a and to an intermediate extent in Group 2b. Changes in effective arterial elastance (afterload) were also different in all three groups (p = 0.01 by ANOVA). Effective arterial elastance was reduced most in Groups 2b and 2a and least in Group 1. Changes in stroke volume differed in all three groups (p = 0.004 by ANOVA). Stroke volume was only reduced in Group 1 and was increased most in Group 2a and to a lesser degree in Group 2b. Reductions in systolic blood pressure differed in all three groups (p = 0.05 by ANOVA). Systolic blood pressure was reduced most in Groups 2a and 1 and least in Group 2b. Thus, patients with a baseline E_a/E_{es} ratio <1 (Group 1) demonstrated a predominant preload reduction but only a modest afterload reduction. In contrast, patients with an E_a/E_{es} ratio >1 and normal or mildly depressed left ventricular ejection fraction (Group 2a) demonstrated a predominant afterload reduction but only a modest preload reduction. Finally, patients with an E_a/E_{es} ratio >1 and low left ventricular ejection fraction (Group 2b) demonstrated significant preload and afterload reductions after bolus injection of intravenous nitroglycerin, but the afterload reduction was predominant, as indicated by an increase in stroke volume. A representative example of pressure-volume relations after bolus intravenous administration of nitroglycerin for a patient in each group is shown in Figure 3.

Discussion

In the present study, patients with an initial E_a/E_{es} ratio <1 (Group 1) constituted a group of normotensive patients with intact systolic function who exhibited a predominant preload reduction, with a decrease in stroke volume in response to bolus intravenous administration of nitroglycerin. Those with an initial E_a/E_{es} ratio >1 and normal to moderately reduced systolic function (Group 2a) constituted a group of patients, most of whom were hypertensive, who had a predominant afterload reduction with an increase in stroke volume after bolus administration of nitroglycerin. Finally, those with an initial E_a/E_{es} ratio >1 and abnormal left ventricular ejection fraction (Group 2b) constituted a group of patients with clinical congestive heart failure who exhibited a reduction in both preload and afterload in response to bolus administration of nitroglycerin but with a predominant reduction in afterload with an increase in stroke volume. Thus, the transient hemodynamic response to bolus intravenous administration of nitroglycerin before the activation of reflexes can be predicted by the baseline relation of afterload to end-systolic elastance and by a clinical characterization (i.e., normotensive versus hypertensive versus congestive heart failure). Few other studies have tested the utility of the effective arterial elastance/end-systolic elastance ratio in normal (20) and abnormal (21) circulations.

Vasodilator therapy for the treatment of congestive heart failure gained initial popularity with the appreciation that the failing left ventricle is exquisitely sensitive to afterload, whereas the normal left ventricle can adjust its contractile state to eject against higher afterload (22,23). Patients in Group 1 had a decrease in stroke volume in response to a decrease in preload (end-diastolic volume). This finding confirms the dependence of ventricles with normal contractility on the Frank-Starling mechanism, or the preload sensitivity of stroke volume. Our study also demonstrated that ventricles with depressed contractility are primarily afterload dependent. Patients in Group 2b, who had a clinical history of congestive heart failure, had an increase in stroke volume in response to a decrease in afterload (E_a) despite a

Table 3. Hemodynamic Responses to Intravenous Bolus Administration of Nitroglycerin

Study Group	EDV (ml)	E_a (mm Hg/ml)	SV (ml)	LVSP (mm Hg)
1 (E_a/E_{es} < 1) (n = 9)	−22 ± 7	−0.32 ± 0.07	−5 ± 4	−30 ± 4
2a (E_a/E_{es} > 1; EF > 40%) (n = 9)	−4 ± 4*	−1.20 ± 0.29*	20 ± 6*	−38 ± 6
2b (E_a/E_{es} > 1; EF < 40%) (n = 9)	−11 ± 3	−1.26 ± 0.26*	9 ± 3*	−20 ± 4†

*p < 0.016 versus Group 1. †p < 0.016 versus Group 2a. Values are expressed as mean value ± SEM. EDV = end-diastolic volume; LVSP = left ventricular systolic pressure; SV = stroke volume; other abbreviations as in Tables 1 and 2.

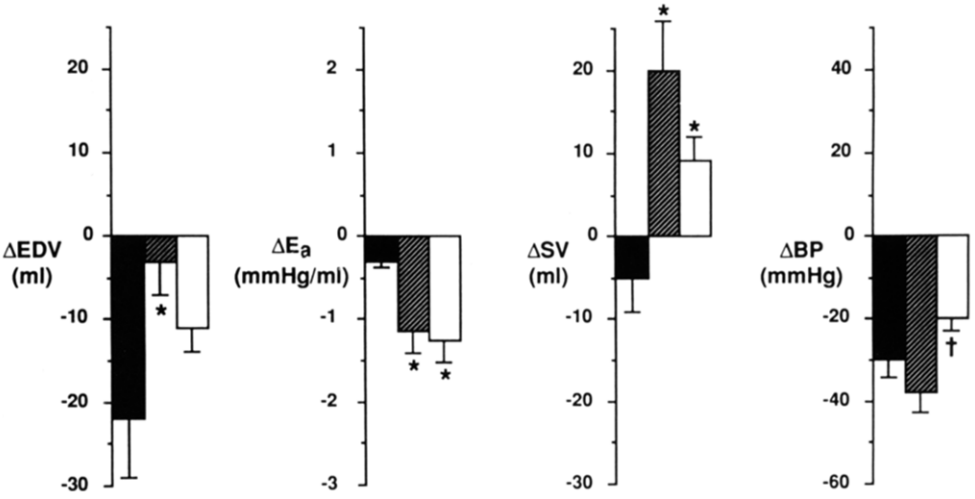
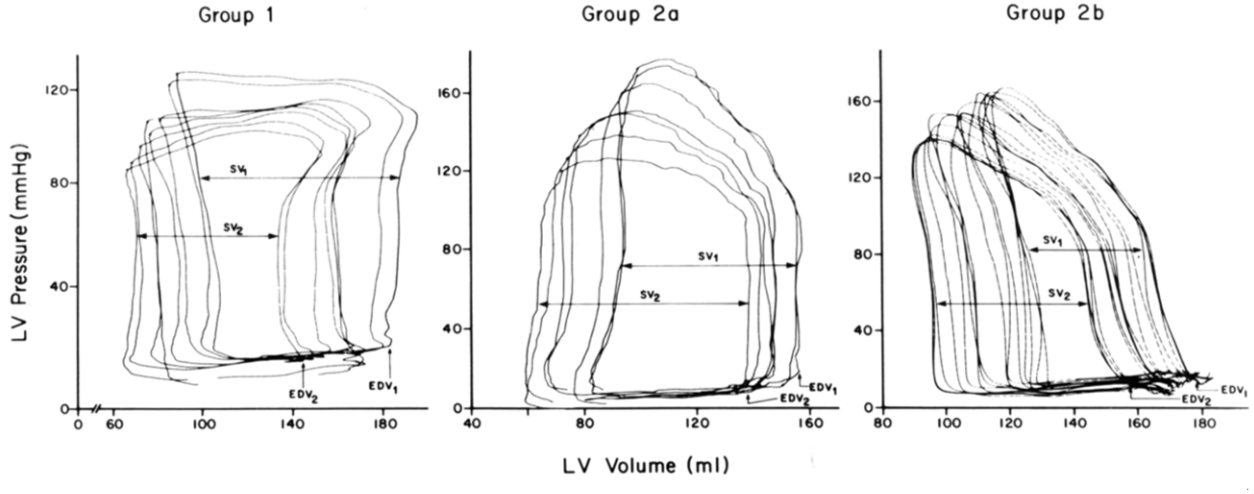


Figure 2. Changes (Δ) in hemodynamic variables after bolus intravenous nitroglycerin in Group 1 (n = 9; E_a/E_{es} <1) (**solid bars**), Group 2a (n = 9; E_a/E_{es} >1; ejection fraction >40%) (**hatched bars**) and Group 2b (n = 9; E_a/E_{es} >1; ejection fraction <40%) (**open bars**). Preload changes, defined as a decrease in end-diastolic volume (EDV) are greatest in Group 1 and intermediate in Group 2b. Afterload changes, defined as a decrease in effective arterial elastance (E_a), are greatest in Groups 2a and 2b. Increases in stroke volume (SV) consistent with a predominant afterload effect are seen in Groups 2a and 2b. Systolic blood pressure (BP) decreased in all groups but to a lesser extent in Group 2b. *$p < 0.05$ vs. Group 1. †$p < 0.05$ vs. Group 2a.

decrease in preload. This observation confirms the dependence of the stroke volume ejected by the failing heart on afterload rather than on preload. Stroke volume increased in patients who did not have congestive heart failure but did have excessive afterload at rest (E_a) (Group 2a). This finding demonstrates the importance of using the framework of ventriculoarterial coupling (E_a/E_{es} ratio) to predict the preload and afterload sensitivity to nitroglycerin in these patients. It might be expected that stroke volume would increase most in patients in Group 2b because they have a clinical history of congestive heart failure and should be the most afterload sensitive of the three groups; however, the increase in stroke volume was similar in patients in Group 2a. Because the decrease in effective arterial elastance was comparable between the two groups, it is possible that patients in Group 2b did not have a larger increase in stroke volume because their reduction in preload was greater than that of patients in Group 2a. This finding could be a reflection of the higher bolus dose of intravenous nitroglycerin administered to Group 2b. Because the absolute preload reduction in Groups 2a and 2b are modest, a more likely explanation for the failure of stroke volume to increase to a greater extent in Group 2b than in Group 2a is the markedly impaired cardiac contractility in the former group. Thus, the impaired myocardium of patients in Group 2b may not have been able to generate a greater augmented stroke volume than seen in patients in Group 2a.

Study limitations. There are several potential limitations to this study. 1) We used volume measurements derived

Figure 3. Representative examples of left ventricular (LV) pressure-volume relations obtained after bolus intravenous administration of nitroglycerin. The patient from Group 1 (E_a/E_{es} <1) demonstrates a large decrease in end-diastolic volume (EDV) and a decrease in stroke volume (SV) from the first (SV_1) to the final (SV_2) beat. The patient from Group 2a (E_a/E_{es} >1; ejection fraction >40%) had a small reduction in end-diastolic volume and an increase in stroke volume from the first (SV_1) to the final (SV_2) beat. The patient from Group 2b (E_a/E_{es} >1; ejection fraction <40%) had a modest reduction in end-diastolic volume and an increase in stroke volume from the first (SV_1) to the final (SV_2) beat.



from the conductance catheter and assumed that the volume corrections for both offset and gain were load independent. Previous investigators (24,25) have shown that, rather than being constants, both the offset and gain corrections may vary somewhat as volume changes. Furthermore, the use of thermodilution-derived stroke volume for gain correction may be inaccurate in patients with depressed left ventricular function (26,27). Despite such limitations, conductance volume measurements are still of value in physiologic studies requiring relative rather than absolute volume measurements (25,28).

2) Nitroglycerin differed in Group 2b from that in Groups 1 and 2a. It has previously been shown (29,30) that low-dose nitrates primarily affect venous capacitance vessels, whereas higher dose nitrates affect the arterial system. To be certain that the response of Group 2b was not due to the higher bolus dose of nitroglycerin administered, an additional three patients with clinical heart failure (left ventricular ejection fraction 23% to 37%) were given both 200- and 400-μg doses of bolus intravenous nitroglycerin. In these three patients, both 200- and 400-μg doses of intravenous nitroglycerin produced qualitatively similar hemodynamic effects, with reductions in preload and afterload and with predominant afterload reductions because stroke volume increased. These data suggest that although patients in Group 2b received a larger dose of nitroglycerin than that of other patients, the predominant preload or afterload effects demonstrated in these patients were not due to this higher dose. Nevertheless, it is possible that even higher doses of bolus intravenous nitroglycerin might have shown a qualitatively different hemodynamic effect from that demonstrated at the doses used in the present study.

3) Patients did not achieve a steady state cardiovascular response to bolus intravenous nitroglycerin at the time of our measurements. This factor is relevant because calculations of end-diastolic volume and effective arterial elastance after bolus intravenous nitroglycerin were made in non-steady state conditions. Despite this limitation, there can be no doubt that both Groups 2a and 2b had predominant decreases in effective arterial elastance because stroke volume increased. Our conclusions are therefore still valid. Furthermore, the effects of nitrates on the peripheral circulation can be affected by reflex activation. Vatner et al. (31) previously demonstrated that cardiac output may initially increase after nitrate administration but subsequently decrease because of reflex activation. A goal of the present study was to circumvent this difficulty by attempting to obtain all hemodynamic measurements before the onset of reflex activation, however, reflex activation apart from that observed by a reflex increase in heart rate may have occurred.

Conclusions. The predominant hemodynamic effect of bolus intravenous nitroglycerin may be predicted by the baseline relation of afterload to ventricular function. Patients with excessive afterload for their level of left ventricular function (E_a/E_{es} ratio >1) develop a predominant afterload reduction in response to nitroglycerin. In contrast, nitroglycerin administration results in a predominant preload reduction in patients whose afterload is not excessive for their level of left ventricular function (E_a/E_{es} ratio <1).

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References

1. Nyberg G, Holmberg B. Haemodynamic, anti-anginal and anti-ischaemic effects of sublingual nitroglycerin: dose-response, duration and time of onset of action. Eur J Clin Pharmacol 1988;34:561–7.
2. Yaginuma T, Avolio A, O'Rourke M, et al. Effect of glyceryl trinitrate on peripheral arteries alters left ventricular hydraulic load in man. Cardiovasc Res 1986;20:153–60.
3. Weaver JC, Willis JH, Hodge HC. The effect on the blood pressure of normal persons and hypertensive patients of glyceryl trinitrate, sodium nitrite, erythrol tetranitrate and mannitol hexanitrate. Am Heart J 1944; 28:601–10.
4. Chrysant SG, Dunn FG, de Carvalho JGR, Adamopoulos PN, Frohlich ED. Action of nitroglycerin and amyl nitrite in labile and essential hypertension. Arch Intern Med 1977;137:1702–5.
5. Imhof PR, Ott B, Frankhauser P, Chu L-C, Hodler J. Difference in nitroglycerin dose-response in the venous and arterial beds. Eur J Clin Pharmacol 1980;18:455–60.
6. Yaginuma T, Avolio A, O'Rourke M, et al. Effect of glyceryl trinitrate on peripheral arteries alters left ventricular hydraulic load in man. Cardiovasc Res 1986;20:153–60.
7. Fitchett DH, Simkus GJ, Beaudry JP, Marpole DGF. Reflected pressure waves in the ascending aorta: effect of glyceryl trinitrate. Cardiovasc Res 1988;22:494–500.
8. Kelly RP, Gibbs HH, O'Rourke MF, et al. Nitroglycerin has more favourable effects on left ventricular afterload than apparent from measurement of pressure in a peripheral artery. Eur Heart J 1990;11:138–44.
9. Latson TW, Hunter WC, Katoh N, Sagawa K. Effect of nitroglycerin on aortic impedance, diameter, and pulse-wave velocity. Circ Res 1988;62: 884–90.
10. Simon AC, Levenson JA, Levy BY, Bouthier JE, Peronneau PP, Safar ME. Effect of nitroglycerin on peripheral large arteries in hypertension. Br J Clin Pharmacol 1982;14:241–6.
11. Smulyan H, Mookherjee S, Warner RA. The effect of nitroglycerin on forearm arterial distensibility. Circulation 1986;73:1264–9.
12. Sunagawa K, Maughan WL, Burkhoff D, Sagawa K. Left ventricular interaction with arterial load studied in isolated canine ventricle. Am J Physiol 1983;245(Heart Circ Physiol 14):H773–H80.
13. Sunagawa K, Maughan WL, Sagawa K. Optimal arterial resistance for the maximal stroke work studied in isolated canine left ventricle. Circ Res 1985;56:586–95.
14. Burkhoff D, van der Velde E, Kass D, Baan J, Maughan WL, Sagawa K. Accuracy of volume measurement by conductance catheter in isolated, ejecting canine hearts. Circulation 1985;72:440–7.
15. Kass DA, Yamazaki T, Burkhoff D, Maughan WL, Sagawa K. Determination of left ventricular end-systolic pressure-volume relationships by the conductance (volume) catheter technique. Circulation 1986;73:586–95.
16. Kass DA, Midei M, Graves W, Brinker JA, Maughan WL. Use of a conductance (volume) catheter and transient inferior vena caval occlusion for rapid determination of pressure-volume relationships in man. Cathet Cardiovasc Diagn 1988;15:192–202.
17. Armstrong PW, Armstrong JA, Marks GS. Pharmacokinetic-hemodynamic studies of intravenous nitroglycerin in congestive cardiac failure. Circulation 1980;62:160–6.

18. Abrams J. Hemodynamic effects of nitroglycerin and long-acting nitrates. Am Heart J 1985;110:216–24.
19. Kennedy JW, Trenholme SE, Kasser IS. Left ventricular volume and mass from single-plane cineangiocardiogdram. Am Heart J 1970;80:343–52.
20. Kass DA, Grayson R, Marino P. Pressure-volume analysis as a method for quantifying simultaneous drug (amrinone) effects on arterial load and contractile state in vivo. J Am Coll Cardiol 1990;16:726–32.
21. Asanoi H, Sasayama S, Kameyama T. Ventricular coupling in normal and failing heart in humans. Circ Res 1989;65:483–93.
22. Sarnoff SJ, Mitchell JH, Gilmore JP, Remensnyder JP. Homeopathic autoregulation of the heart. Circ Res 1960;8:1077–91.
23. Franciosa JA, Guha NM, Limas CJ, Rodriguera E, Cohn JN. Improved left ventricular function during nitroprusside infusion in acute myocardial infarction. Lancet 1972;1:650–4.
24. Boltwood CM Jr, Appleyard RF, Glantz SA. Left ventricular volume measurement by conductance catheter in intact dogs. Parallel conductance volume depends on left ventricular size. Circulation 1989;80:1360–77.
25. Applegate RJ, Cheng CP, Little WC. Simultaneous conductance catheter and dimension assessment of left ventricle volume in the intact animal. Circulation 1990;81:638–48.
26. van Grondelle A, Ditchey RV, Groves BM, Wagner WW Jr, Reeves JT. Thermodilution method overestimates low cardiac output in humans. Am J Physiol 1983;245:H690–3.
27. Cigarroa RG, Lang RA, Williams RH, Bedotto JB, Hillis LD. Underestimation of cardiac output by thermodilution in patients with tricuspid regurgitation. Am J Med 1989;86:417–20.
28. Burkhoff D. The conductance method of left ventricular volume estimation. Methodologic limitations put into perspective. Circulation 1990;81:703–6.
29. Abrams J. Hemodynamic effects of nitroglycerin and long-acting nitrates. Am Heart J 1985;110:216–24.
30. Abrams J. Glyceryl trinitrate (nitroglycerin) and the organic nitrates: choosing the method of administration. Drugs 1987;34:391–403.
31. Vatner SF, Pagani M, Rutherford JD, Millard RW, Manders WT. Effects of nitroglycerin on cardiac function and regional blood flow distribution in conscious dogs. Am J Physiol 1978;234(Heart Circ Physiol 3):H244–52.